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Can repetitive transcranial magnetic stimulation promote recovery of consciousness in patients with disorders of consciousness? A randomized controlled trial

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ABSTRACT

Background: Disorders of consciousness (DoC) are characterized by a broad decline in background excitatory synaptic activity and varying levels of cerebral network disruption. Repetitive transcranial magnetic stimulation (rTMS), a neuromodulatory technique, is anticipated to assist the recovery of consciousness. Nonetheless, ongoing debates persist regarding its effectiveness, in light of the inconsistent results of recent research.
Objective: The purpose of this study is to investigate the efficacy of rTMS in promoting recovery of consciousness in patients with DoC and to probe its impact on activity of cerebral functional networks.
Methods: Forty-eight patients with DoC were included in this randomized controlled trial (Chinese Clinical Trial Registry: ChiCTR2100044930). Twenty-four patients in the control group accepted conventional therapy. Another 24 patients in the rTMS group received extra rTMS over the dorsolateral prefrontal cortex (DLPFC) once per workday during a 4-week intervention phase. Primary outcome was the proportion of patients emerging improvement on level of consciousness (LOC) based on coma recovery scale- revised (CRS-R) at the end of intervention. Furthermore, other behavioral scales such as the clinical global impression-improvement (CGI-I) and resting state-electroencephalography (rs-EEG) microstate were employed as secondary outcomes. Different microstates served as tools to detect the activity of respective corresponding resting state cerebral functional networks.
Results: In comparison to the control group, the rTMS group exhibited a higher proportion of patients emerging improvement on LOC at post-intervention, with a risk ratio of 3.06 (95 % CI 1.54 to 6.09, $P = 0.001$). The distribution of patients with each grade of CGI-I across the groups also implied a trend that favored the rTMS group (common odds ratio:0.20, 95 % CI 0.065 to 0.63, $P = 0.006$). With respect to microstate E, the rTMS group had a significantly reduced global explained variance (GEV) was observed in the rTMS group ($Z = -2.61$, $P_{bonf} = 0.027$).
Conclusion: High-frequency rTMS over the DLPFC could promote recovery of consciousness in patients with DoC. It might get involved in modulating the balance among cerebral functional networks and facilitating consciousness recovery.

Abbreviations: CGI-I, clinical global impression-improvement; CI, confidence interval; CRS-R, coma recovery scale- revised; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; DoC, Disorders of consciousness; GEV, global explained variance; LOC, level of consciousness; rs-EEG, resting state- electroencephalography; rTMS, repetitive transcranial magnetic stimulation.

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1. Introduction

Disorders of consciousness (DoC) are defined by decreased wakefulness and/or awareness (Sergi & Bilotta, 2020), commonly resulting from severe neurological injuries such as traumatic brain injury (TBI), stroke, or hypoxic-ischemic encephalopathy (HIE). According to the degree of preservation or restoration of wakefulness and awareness, patients with DoC can be categorized into distinct stages of consciousness recovery, such as coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS) (Giacino et al., 2002; Laureys et al., 2010; Bruno et al., 2011). The absence of consciousness predisposes them to secondary complications across other systems, such as pulmonary infections, gastrointestinal dysfunctions, and intensive care unit-acquired weakness (Ganesh et al., 2013; Whyte & Nakase-Richardson, 2013). This not only considerably impedes their overall recovery but also amplifies the difficulties associated with nursing care and increases healthcare costs. Meanwhile, a considerable number of these patients, due to their varying levels of lack of mobility and communication capabilities, could be misdiagnosed in their conditions (Schiff, 2015; Owen, 2019; Thibaut et al., 2021), further complicating the formulation of an individualized intervention protocol. Hence, the exploration of approaches that facilitate the recovery of consciousness is of utmost importance.

With advancements in neuroscience, remarkable potential has been exhibited by neuromodulation in promoting the recovery of consciousness (Thibaut et al., 2019; Edlow et al., 2021). According to the current pathological hypotheses of DoC (Giacino et al., 2014), the recovery of consciousness is contingent upon the restoration of activities of cortex, thalamus, striatum, and other neuronal nuclei, as well as the resurgence of dynamic interaction among various brain networks, including the Mesocircuit, and the Ascending Reticular Activating System (ARAS). The Mesocircuit model primarily centers on repairing the central thalamus and its frontostriatal connections, which are crucial for functional network connectivity associated with intrinsic thoughts and extrinsic stimuli (Schiff, 2010; Schiff, 2023). The ARAS, on the other hand, primarily focuses on determining whether it provides sufficient input to the mesocircuit and other higher-order brain networks (Edlow et al., 2013; Kovalzon, 2016), such as the fronto-parietal network (FPN) and sensorimotor network (SMN), to induce depolarization of cortical neurons. Both the Mesocircuit and the ARAS serve as the foundation for a diverse range of neuromodulation techniques and motivate distinct directions of clinical research. Among them, transcranial magnetic stimulation (TMS), as a non-invasive neuromodulation technique, has attracted substantial attention due to its safety, economics, and convenience.

TMS utilizes alternating magnetic fields placed on the scalp, leveraging electromagnetic induction principles to generate induced currents within the cortex, which further modulate cortical neuron activity (Chervyakov et al., 2015). Depending on stimulation paradigms, TMS can be categorized into Single-Pulse TMS (sTMS), repetitive TMS (rTMS), and Theta Burst Stimulation (TBS), among other forms. Of these, rTMS, through varied stimulation locations and frequencies, can induce or suppress local or remote activity of the cortical neuron (Hoogendam et al., 2010). By modifying long-term synaptic excitability, rTMS could enhance neural plasticity and facilitate the reorganization of cerebral network (Pell et al., 2011). A previous case report had indicated that a six-week course of rTMS could notably facilitate the recovery of a patient with VS/UWS after severe TBI (Louise-Bender Pape et al., 2009). Nevertheless, ongoing debates persist regarding the effectiveness of rTMS in promoting recovery of consciousness in patients with DoC, especially in light of the inconsistent results of recent randomized controlled trials.

Overall, the target selection of prior rTMS studies mainly focused on the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC). Regarding the research targeting M1 for the treatment of DoC, several rTMS studies have been reported in recent years, but the certainty of its efficacy remains somewhat controversial (Cincotta et al., 2015; He et al., 2018; Shen et al., 2023). On the other hand, rTMS studies that targeted the DLPFC have produced encouraging improvements in the scores of behavioral scales (Zhang et al., 2021; Chen et al., 2022; Fan et al., 2022). DLPFC, as a key node in the FPN, plays an important role in regulating environmental awareness, decision-making, and balancing the prefrontal cortex networks (Menon & D'Esposito, 2022). However, most of these studies targeting DLPFC utilized the advancement of the total score of coma recovery scale-revised (CRS-R) as their primary outcome. Notably, given the nonlinear relationship that exists between the total score of CRS-R and individual LOC (Sattin et al., 2015), a minor elevation of the score may not substantially indicate an improvement on the LOC (Monti et al., 2023).

Additionally, the predominant approach of investigating the neurophysiological mechanisms that prompt consciousness recovery in previous rTMS studies was to compare the spectral power (i.e., power spectral density of band δ, θ, α, β, and γ) of resting state-electroencephalography (rs-EEG) in isolated brain regions (He et al., 2018; Xu et al., 2023). Nevertheless, recent evidence suggests that the formation of consciousness does not stem from single brain areas or networks. Instead, it arises from various modules, functional networks, and hierarchical structures spread throughout the brain (Koch et al., 2016; McKilliam, 2020). Hence, assessing local brain activity in isolation might fail to capture the entire variation of the brain along with consciousness restoration. Moreover, several works in the literature suggest that spontaneous consciousness could be considered as a dynamic process of a chain of discrete mental events (Meehan & Bressler, 2012; Michel & Koenig, 2018). Individuals with intact consciousness possess the ability to flexibly transition between mental events, whether these are triggered by intrinsic thoughts or external stimuli. Therefore, considering the deficiency of spectral power, which presumes that all processes share the same temporal dynamics, it might be advantageous to employ other indicators that could reflect the global dynamic alterations of the brain to track the fluctuation of LOC.

EEG microstate, as determined by scalp electric field distributions, refers to a relatively stable scalp topographical structure maintained for a short period (Lehmann et al., 1987). Each microstate lasts for a subsecond scale before transitioning into another stable state (Michel & Koenig, 2018). According to the "neuronal workspace model" reported by Dehaene et al., neurons from various brain regions simultaneously co-activate and establish discrete large-scale spatio-temporal neural networks (Dehaene et al., 2003). Similarly, these spatio-temporal networks remain stable within a time frame and quickly transition into a renewed co-activation structure. As a result, the microstate, being linked to large-scale resting-state cerebral functional networks, could serve as an elemental component of consciousness (Khanna et al., 2015).

In light of these findings, the aim of this study is to investigate whether rTMS could promote recovery of consciousness in patients with DoC. Moreover, rs-EEG microstate was utilized to further investigate the impact of rTMS on activity of cerebral functional networks in patients with DoC.

2. Methods

2.1. Study design

This was a multi-center, randomized, blank-controlled, parallel design clinical study. The study was registered at the Chinese Clinical Trial Registry (ChiCTR2100044930) and conducted following the Declaration of Helsinki. It has received approval from the Ethics Committee of the coordinating center (2021-SR-046). Prior to the commencement of this trial, the patient's legal guardian voluntarily signed voluntary written informed consent.

2.2. Participants

Patients with DoC who were hospitalized to the First Affiliated

Table 1
Trial inclusion, exclusion, and withdrawal criteria.

Inclusion criteria	Rational for inclusion
1. Based on CRS-R, patients who were diagnosed with coma, VS/UWS, and MCS.	Population of interest
2. Adult patients aged 18 years or older.	Population of interest
3. Patients whose disease duration was greater than 1 month and less than 1 year.	Population of interest
4. Complete absorption of all cerebral hemorrhage lesions for patients diagnosed with intracranial hemorrhage.	Population of interest
5. The guardian allowed the patient to participate and signed written informed consent.	Ethical requirement
Exclusion criteria	**Rational for exclusion**
1. Refused randomization.	Ineligible for enrolment
2. Diagnosed with HIE.	Ineligible for enrolment
3. With neural stimulators such as deep brain stimulation, spinal cord stimulation, and others.	Ineligible for enrolment
4. With a personal history of epilepsy, a family history of idiopathic epilepsy, or the use of epileptogenic drugs, as confirmed by EEG showing epileptiform discharges.	Ineligible for enrolment
5. With intracranial shunt, metallic aneurysm clip, metallic pin, or vascular stapler.	Protocol violation
6. With an implanted cardiac pacemaker, cardiac catheter, or electronic pump.	Protocol violation
7. Patients in whom the rTMS stimulation site involves using a metal plate to close cranial defects.	Protocol violation
8. With complications such as acute myocardial infarction, pulmonary embolism, acute infection, sepsis, severe anemia, and others.	Protocol violation
9. With other serious systemic diseases or clinically critical conditions, including unstable respiratory or hemodynamic conditions.	Protocol violation
Withdrawal criteria	**Rational for withdrawal**
1. The patient's guardian makes such a request.	Relative desire
2. The patient develops a severe disease, such as stroke, pulmonary infection, or severe systemic illness, and continuing participation could be risky to the patient according to the opinion of investigator or doctor.	Negative physical condition
3. The patient develops a severe adverse reaction related to the rTMS.	Severe adverse event

Abbreviations: CRS-R, Coma recovery scale-revised; EEG, electroencephalography; HIE: hypoxic-ischemic encephalopathy; MCS, minimally conscious state; rTMS, repetitive transcranial magnetic stimulation; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

Hospital of Nanjing Medical University, Nanjing Zijin Hospital, and Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University were prospectively recruited. Consolidated criteria for patients' enrolment were summarized in Table 1. A baseline LOC of each patient was determined by the best of three intermittent CRS-R performed within one-week before study enrollment.

2.3. Interventions

Eligible participants were randomly allocated to either the rTMS or control group, using a 1:1 allocation ratio. Participants in the control group received no additional intervention beyond basic drug therapy, hyperbaric oxygen, and conventional rehabilitation therapy. Participants in the rTMS group received extra rTMS once per working day (from Monday to Friday) 10-min session throughout 4 weeks. rTMS was conducted by using a Magneuro100Mate device (manufactured by VISHEE Company, Nanjing, China) and an eight-shaped coil (model VCY001). According to the recommendation of the International Federation of Clinical Neurophysiology (Rossini et al., 2015), the stimulation intensity of rTMS was established based on the resting motor threshold (RMT) of each patient. It refers to the minimal stimulation intensity necessary to produce motor evoked potentials with amplitudes exceeding 50 μV in at least 5 out of 10 stimuli of the target muscle, typically the abductor pollicis brevis, during stimulation on M1.

An eight-shaped coil was positioned at an angle of 45°to the skull's mid-line over the unaffected side of the DLPFC, according to the international 10–20 EEG system (Seeck et al., 2017). As shown in Fig. 1, The rTMS procedure consisted of a session of 2,000 pulses delivered in 40 trains of 10 Hz (Hz) at an intensity of 90 % RMT. Each train lasted 5 s with a 10 s interval between each other.

2.4. Outcomes

Clinical behavioral scales were assessed at baseline (Week 0), after completion of the intervention (Week 4), and at the 4-week post-intervention follow-up (Week 8). rs-EEG were collected at Week 0 and 4.

2.4.1. Primary outcome

The primary outcome was the proportion of patients emerging improvement on LOC at Week 4 (defined as a progression from a lower LOC to a superior one). CRS-R (Giacino et al., 2004), as a widely applied bedside behavioral assessment tool, was employed. The comprehensive consideration of scores across its six sub-scales allowed classification of patients' LOC into four distinct stages: coma, VS/UWS, MCS, and emergence from minimally conscious state (EMCS). A patient in EMCS is considered to have full consciousness, despite potential variations in motor and cognitive impairments (supplementary table S1).

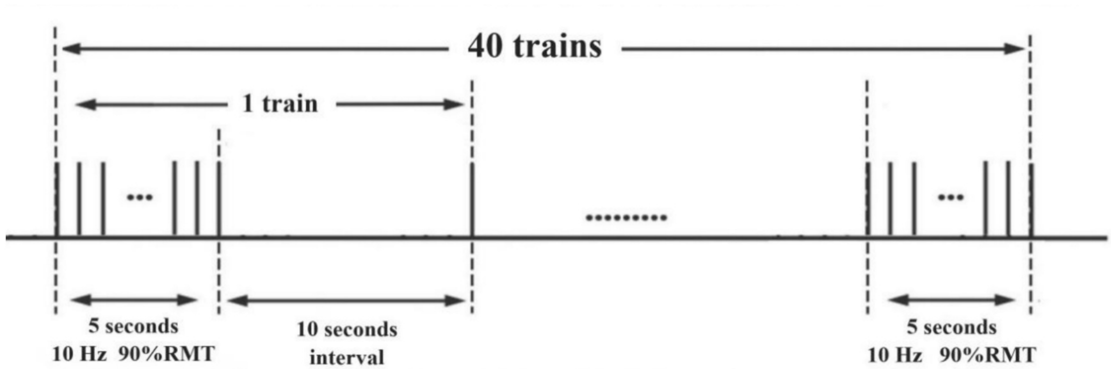

Fig. 1. Details of rTMS procedure. Each session contains 40 trains, with each train containing 5 s of stimulation time and 10 s of rest interval. The stimulation intensity is 90 % RMT, with a stimulation frequency of 10 Hz, totaling 2000 pulses. Abbreviations: Hz, hertz; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation.

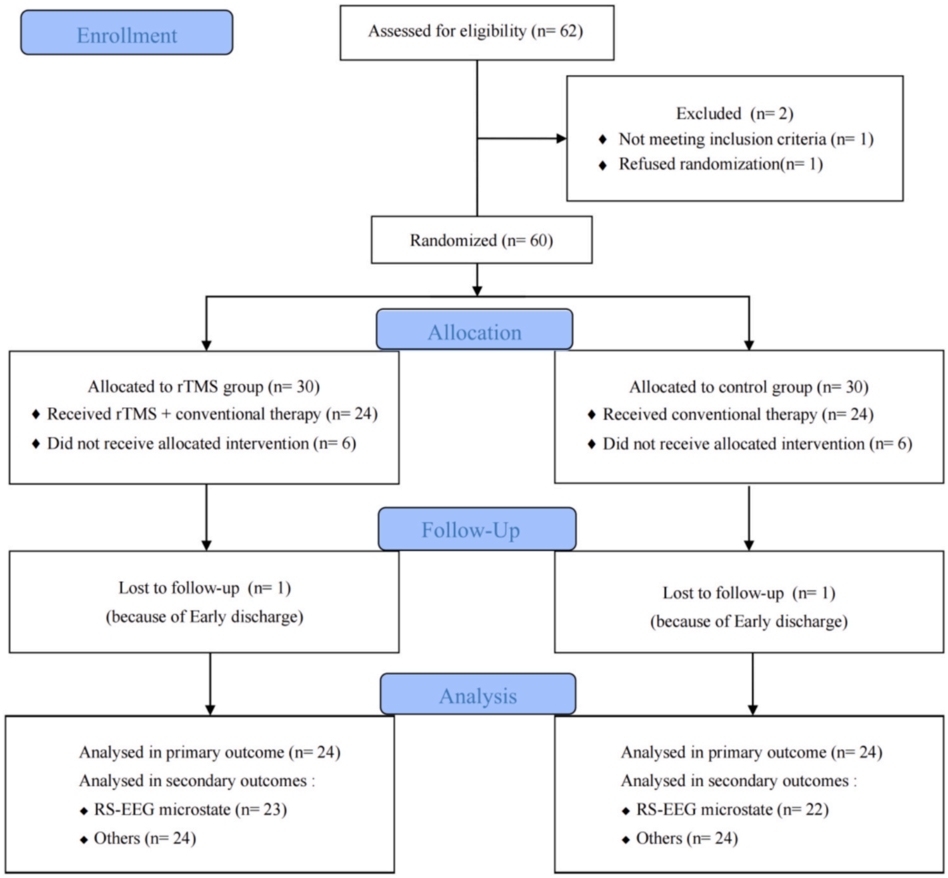

Fig. 2. Flow diagram of the study Follow Consolidated Standards of Reporting Trials (CONSORT) 2010 Flow diagram Abbreviations: RS-EEG: resting state-electroencephalography; rTMS: repetitive transcranial magnetic stimulation.

Table 2
Baseline demographics and clinical behavioral characteristics of the study population*.

Patient characteristics	Total patients (n = 48)	rTMS group (n = 24)	control group (n = 24)	P value
Age in year, mean ± SD	54.1 ± 16.2	52.2 ± 15.8	56.0 ± 16.6	0.417
Gender, n (%)				0.505
Male	36 (75.0)	19 (79.2)	17 (70.8)	
Female	12 (25.0)	5 (20.8)	7 (29.2)	
Days from injury to randomization, median (IQR)	63.5 (44.3, 90.5)	65.0 (41.0, 91.8)	61.5 (45.8, 84.5)	0.765
Etiology, n (%)				0.745
TBI	35 (72.9)	17 (70.8)	18 (75.0)	
Non-TBI	13 (27.1)	7 (29.2)	6 (25.0)	
Level of consciousness, n (%)				0.812
Coma	4 (8.33)	2 (8.30)	2 (8.30)	
VS/UWS	29 (60.4)	15 (62.5)	14 (58.3)	
MCS	15 (31.3)	7 (29.2)	8 (33.3)	
Score of GCS, mean ± SD	7.46 ± 2.18	7.42 ± 2.28	7.50 ± 2.13	0.896

* Values were means ± standard deviations, counts (percentages), and medians (inter-quartile ranges).
Abbreviations: CRS-R, Coma recovery scale-revised; IQR, inter-quartile ranges; MCS, minimally conscious state; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; TBI, traumatic brain injury; VS/UWS, vegetative state/ unresponsive wakefulness syndrome.

2.4.2. *Secondary outcome*

The secondary outcomes consist of: the proportion of patients emerging improvement on LOC at Week 8; the grade of the LOC, the score of Glasgow Coma Scale (GCS), and the grade of Clinical global impression-improvement (CGI-I) at Week 4 and 8; the features of rs-EEG microstate at Week 4.

Individual LOC was categorized into four stages, denoted as grade 1 through 4, corresponding to coma, VS/UWS, MCS, and EMCS, respectively. A higher grade signifies a more advanced restoration of consciousness. Moreover, we employed the GCS and CGI-I, widely recognized clinical bedside assessment tools, to monitor the outcomes of patients. The GCS is frequently employed by medical staff to evaluate the status and severity of coma in individuals suffering from acute brain injuries (Teasdale & Jennett, 1974). It comprises three components: eyes opening response, verbal response, and motor response, with a total score between 3 and 15. A reduced score correlates with a more profound level of DoC. The CGI-I serves as a tool for judging the overall clinical enhancement of patients, conducted by caregivers closely monitoring the patient over a long period (Guy, 1976). The scoring system on this scale ranges between 1 and 7, with a lower score indicating a higher degree of improvement in the patient's comprehensive condition.

2.4.3. *rs-EEG recording and microstate analysis*

Our study employed a 30-channel system following the international 10–10 standard system to collect a 10-minute rs-EEG data from patients with DoC (Seeck et al., 2017). The corresponding electrode positions was exhibited in the supplementary figure S1. Data was collected with an online sampling rate set at 250 Hz and the electrode Cz was set as online reference. For non-comatose patients, a standard procedure (by

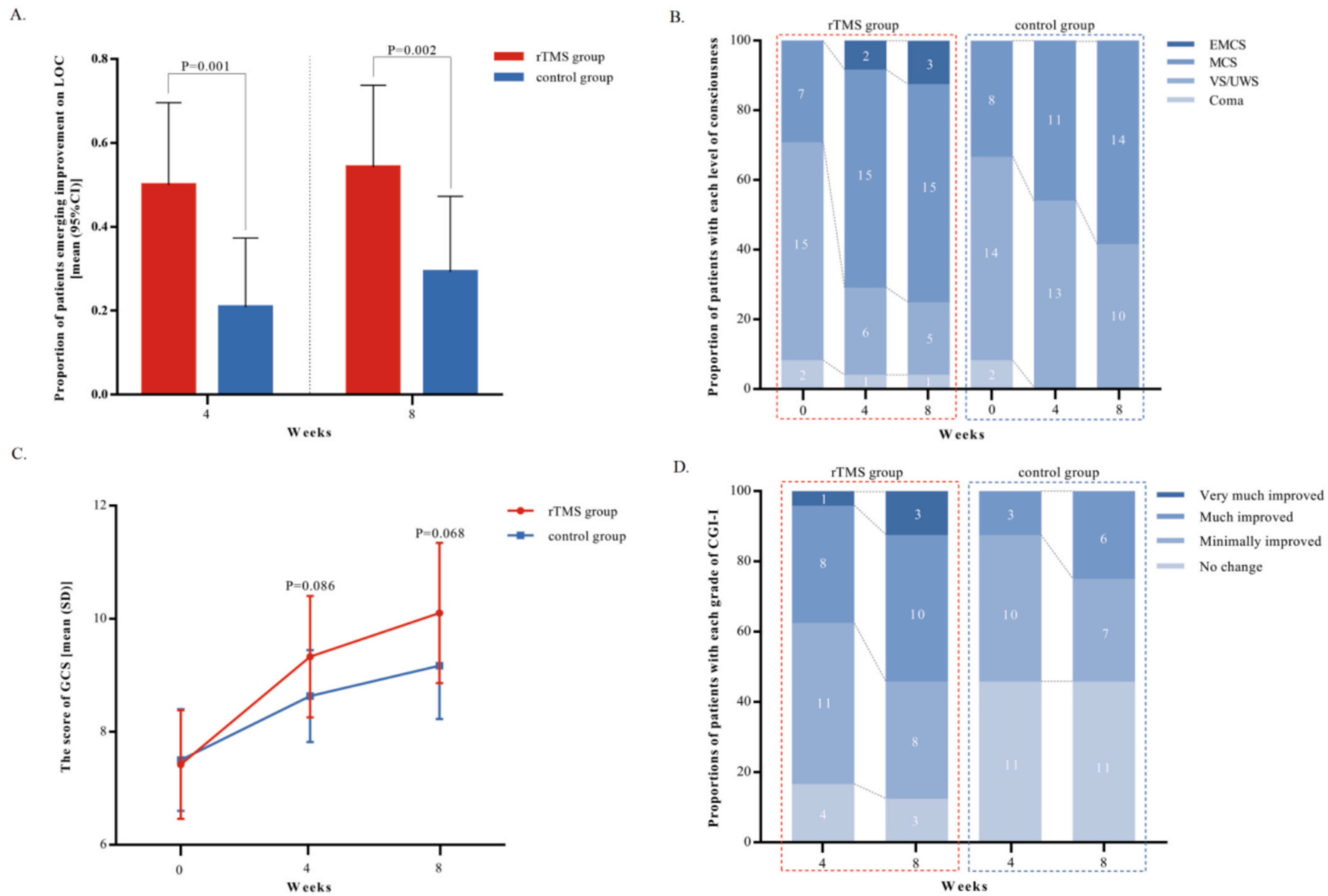

Fig. 3. Behavioral results of the two groups at different time points* Based on the CRS-R, the proportions of patients emerging improvement on LOC in both groups at Week 4 and 8; Based on the CRS-R, the proportions of patients with each level of consciousness in both groups at Week 0, 4, and 8; The means of GCS score and its standard deviation of patients in both groups at Week 0, 4 and 8; The proportions of patients with each grade of CGI-I in both groups at Week 4 and 8. * The value with white color in each column represents its absolute amount in each corresponding category. Abbreviations: CGI-I, clinical global impression- improvement; CRS-R, coma recovery scale-revised; GCS, Glasgow Coma Scale; LOC, level of consciousness; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.

verbal or tactile stimulation) based on CRS-R was employed to ensure they were awake with their eyes open (Giacino et al., 2004).

MNE-python (version 1.7.0) was used to preprocess the collected EEG data (Larson et al., 2024). Data quality was firstly evaluated through a combination of the automatic threshold method and visual inspection. In cases where the EEG data exhibited no more than three bad channels, these were discarded, and spherical spline interpolation was implemented, utilizing the remaining channels (Perrin et al., 1987). To eliminate signal artifacts caused by eyes-blink, heartbeat, line noise, and other potential forms, independent component analysis was applied (Ablin et al., 2018). Data was subsequently re-referenced to common average after being band-pass filtered between 2 and 20 Hz.

The Cartool software was utilized to conduct the microstate analysis (Brunet et al., 2011). To avoid losing microstate features triggered by simultaneous processing of EEG data collected at distinct time points, we divided all the preprocessed EEG data into the baseline group and post-intervention group, respectively. For every sampling point, the global field power (GFP) was firstly computed. Next, templates with high GFP were randomly selected and clustered by using a polarity-insensitive modified k-means algorithm (Pascual-Marqui et al., 1995). The k-range was established from 3 to 8 and four topographic maps that possessed a high Global Explanatory Variance (GEV) were established in each group. The GEV describes the variance ratio of a specific topographic map in explaining EEG data, thus representing the interpretive capacity of the microstate for the whole EEG signal. Finally, the four topographic maps were back-fit to each original EEG data by using a winner-take-all strategy. Three temporal dynamic features were further extracted from the microstate time series: coverage, mean duration, and occurrence. The coverage indicates the percentage of the whole recording duration that a certain microstate takes up. The mean duration implies the average time that a microstate remains in an active state, expressed in milliseconds (ms). The occurrence provides the count of the microstate's repetitions within a specified epoch, represented in Hz. Besides, the LORETA software (Version 20081104) and an MNI 152 template head MRI were used to reconstruct the source space imaging of each microstate (Pascual-Marqui et al., 1994; Pascual-Marqui, 2002).

2.5. Sample size

A sample size of 24 patients per group was required to have an alpha error of 5 % and a power of 80 % to detect 30 % of patients in the rTMS group who appeared advancement on LOC at T1, based on the results of a previously published study. Considering a 20 % participant dropout, a total of 60 participants constituted the sample size, with 30 participants needed for each group. The statistical power was calculated on the basis of a Z test with G*Power software (Version 3.1.9.7).

2.6. Randomization and blinding

Randomization procedure was conducted by the Department of Rehabilitation Medicine from the First Affiliated Hospital of Nanjing Medical University. A 1:1 block randomization assignment divided the

Table 3
Treatment effects for behavioral assessments.

Outcomes	rTMS group (n = 24)	control group (n = 24)	Effect Variables	Between-group differences (95 % CI)	P value
Primary outcome					
Proportion of patients emerging improvement on LOC, n (%)			RR*		
Week 0	–	–		–	–
Week 4	12.0 (50.0 %)	5.00 (20.8 %)		3.06 (1.54 to 6.09)	0.001
Secondary outcomes					
Proportion of patients emerging improvement on LOC, n (%)			RR*		
Week 0	–	–		–	–
Week 8	13.0 (54.2 %)	7.00 (29.2 %)		2.37 (1.36 to 4.14)	0.002
The grade of LOC, median (IQR)			cOR†		
Week 0	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)		–	–
Week 4	3.00 (2.00, 3.00)	2.00 (2.00, 3.00)		4.48 (1.62 to 12.4)	0.004
Week 8	3.00 (2.25, 3.00)	3.00 (2.00, 3.00)		3.89 (1.23 to 12.3)	0.021
The score of GCS, mean ± SD			MD#		
Week 0	7.42 ± 2.28	7.50 ± 2.13		–	–
Week 4	9.33 ± 2.55	8.63 ± 1.93		0.84 (−0.21 to 1.88)	0.113
Week 8	10.1 ± 2.94	9.17 ± 2.24		1.11 (−0.18 to 2.39)	0.090
The grade of CGI-I, mean ± SD			cOR†		
Week 0	–	–		–	–
Week 4	2.75 ± 0.79	3.33 ± 0.70		0.20 (0.065 to 0.63)	0.006
Week 8	2.46 ± 0.88	3.21 ± 0.83		0.13 (0.037 to 0.45)	0.001

* Risk Ratio based on modified Poisson regression;
† common Odds Ratio based on ordered logistic regression;
# Mean difference based on linear regression.
Abbreviations: CGI-I: clinical global impression- improvement; CI: confidence interval; cOR: common odds ratio; GCS: Glasgow Coma Scale; IQR: interquartile ranges; LOC: level of consciousness; MD: mean difference; RR: risk ratio; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation

eligible patients into two groups, with alternating random block sizes (4 to 8). According to the respective group allocation letter (A or B) created by the computer, research personnel assigned participants to the 2 groups according to the random sequence.

Since no sham stimulation was applied to the control group in this study, both the patients' guardian and the physical therapists who administered rTMS were aware of the patients' group assignments. To enhance the reliability of the results under this limitation, an evaluator-blinding design (single-blind) was adopted to minimize potential bias from evaluators' subjective tendencies.

2.7. Statistical methods

Statistical analysis was performed on the collected data using SPSS version 22.0. A two-sided test was used to assess each statistical hypothesis, with a significance threshold of 0.05 being used for statistical significance. Count data was presented as counts (percentages), and baseline comparisons were conducted using a Fisher's exact test or Chi-squared test. Continuous data was exhibited as means ± standard deviations (mean ± SD) or medians (inter-quartile ranges) [median (IQR)] and compared by using an independent sample *t*-test or Mann-Whitney *U* test at baseline.

The full analysis set (FAS), which consists of patients who had been randomized and had received an allocated intervention for at least one week, was used for the main analyses. To account for missing values, multiple imputation using chined equations was utilized. Generalized linear model (GLM) with modified Poisson regression was applied to compare the proportion of patients emerging improvement on LOC, adjusting for potential prognostic imbalance variables: time from injury to randomization, etiology, and initial LOC at baseline. The microstate features were compared between groups by using an independent sample *t*-test or Mann-Whitney *U* test. The correlation between individual microstate features and the total score of CRS-R was evaluated by using Pearson or Spearman correlation analysis. Bonferroni correction was applied to reduce the probability of type I errors brought by multiple comparisons. The remaining outcomes were estimated for between-group differences with mixed effects ordered logistic regression or analysis of covariance (ANCOVA), adjusting for potential imbalance variables.

3. Result

3.1. Participants

As is shown in Fig. 2, 62 patients with DoC were evaluated for eligibility. Among them, 60 patients were randomly allocated to the rTMS (n = 30) or control group (n = 30). Twelve patients were withdrawn during the intervention period and an additional 2 during the follow-up period. Consequently, 48 patients across the two groups were included in analysis. Baseline demographic and clinical characteristics of the 48 patients were well-balanced between groups (See Table 2).

3.2. Primary outcome

Overall, 17 (35.4 %) of the 48 patients were observed improvement on their LOC at Week 4 as measured by CRS-R. Based on the progression of CRS-R scores between baseline and Week 4, the change in CRS-R scores for the rTMS group was 2.0 (0.25, 9.25), while the change in CRS-R scores for the control group was 0.5 (0.00, 2.00). Analysis of individual alteration on LOC among the groups revealed that 9 patients in the rTMS group advanced to a MCS at Week 4, in contrast to only 3 in the control group. Notably, as shown in Fig. 3B, transition to an EMCS was exclusively observed in the rTMS group, involving patients initially diagnosed with a VS/UWS and a MCS. (Supplementary table S2 provided detailed insights into the individual scores from the 6 subscales, and the inferred LOC at different time points.).

The absolute between-group difference in the proportion of patients emerging improvement on LOC at Week 4 was 29.2 % [95 % confidence interval (CI) 3.40 % to 54.9 %] in favor of the rTMS group (12/24, 50.0 %) rather than the control group (5/24, 20.8 %), with an RR of 3.06 (95 % CI 1.54 to 6.09, P = 0.001) (Table 3, Fig. 3A).

3.3. Secondary outcomes

Table 3 and Fig. 3 presents the results for secondary behavioral outcomes. According to the CRS-R during the follow-up period, the proportion of patients emerging improvement on LOC in the rTMS group (13/24, 54.2 %) was significantly higher than that in the control group (7/24, 29.2 %) at Week 8, with an RR of 2.37 (95 % CI 1.36 to 4.14, P = 0.002) (Table 3, Fig. 3A).

Further analysis shows that, as shown in Fig. 3B, there existed a consistent shift towards superior LOC in favor of the rTMS group. The cOR at Week 4 and 8 were 4.48 (95 % CI 1.62 to 12.4, P = 0.004) and 3.89 (95 % CI 1.23 to 12.3, P = 0.021), respectively.

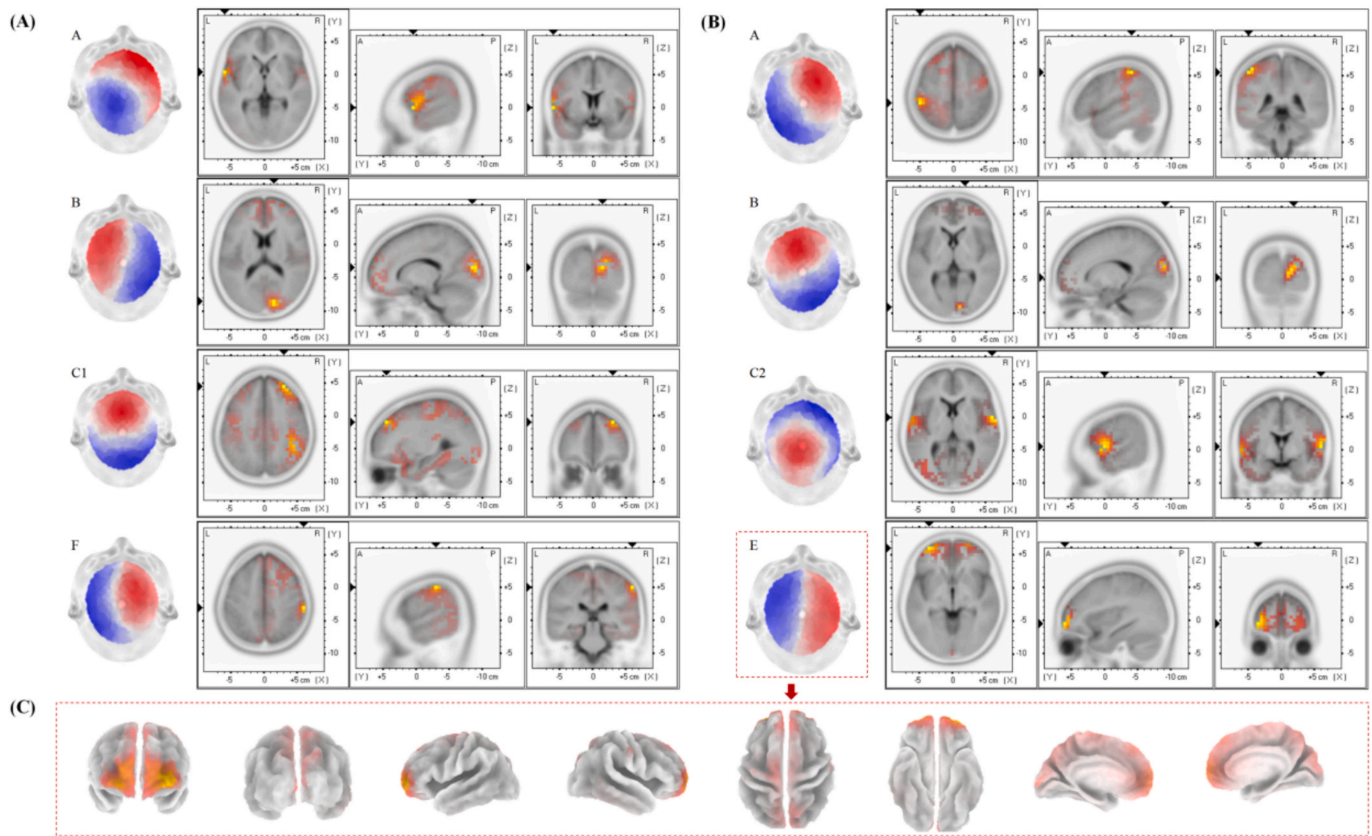

Fig. 4. 2D microstate topographic maps and their respective source space imaging slices at different time points* * Fig. 4A and 4B respectively show the four microstate topographic maps and their respective source space imaging slices at baseline and post-intervention. Each microstate is classified into a specific category according to the spatial structure of its topography. Among them, microstate C1 and C2 are two subtypes of the typical microstate C. Microstates F and E exist only at time points before or after intervention, respectively. Fig. 4C shows the source imaging results of microstate E from different perspectives. Baseline 2D microstate topographic maps (leftmost column) and their respective source space imaging slices (three columns on the right); Post-intervention 2D microstate topographic maps (leftmost column) and their respective source space imaging slices (three columns on the right); Source space distribution of microstate E at the end of the intervention, displays a range of perspectives: anterior, posterior, left-sided, right-sided, superior, inferior, as well as a right-sided view focused on the left hemisphere alone, and a left-sided view of the right hemisphere exclusively.

In contrast with the control group, no significant distinctions were found for the score of GCS although a trend favoring the rTMS group was observed (Week 4: MD:0.84, 95 % CI −0.21 to 1.88, P = 0.113; Week 8: MD: 1.11, 95 % CI –0.18 to 2.39, P = 0.090) (Fig. 3C). Instead, significant differences emerged among groups regarding the distribution of the grade of CGI-I, favoring the rTMS group (Week 4: cOR:0.20, 95 % CI 0.065 to 0.63, P = 0.006; Week 8: cOR: 0.13, 95 % CI 0.037 to 0.45, P = 0.001) (Fig. 3D).

3.4. *Resting-State EEG microstate*

Three of the 48 patients were excluded from microstate analysis due to poor EEG signal quality. The remaining 45 patients continued to maintain the between-group balance in terms of demographic and behavioral characteristics (Supplementary table S3).

Utilizing the rs-EEG data collected at baseline and post-intervention, eight 2D microstate topographic maps and their respective source space imaging slices were constructed (Fig. 4). The optimal cluster number for microstates was identified as 4, accounting for a GEV of 70.7 % and 71.6 %, respectively. Through observing the spatial similarity of topographic structure and canonical microstate model, we discerned that microstate A (left–right orientation), B (right-left orientation), and C (anterior-posterior orientation) could be corresponded respectively to the first three rows of topographic maps in Fig. 4A and 4B. Additionally, the remaining two microstates were also be aligned with microstate E and F, as suggested in previous research.

Upon comparing microstate features at distinct time points, it was found that no indicator for any of the four baseline microstates showed a significant between-group difference (Supplementary table S4). However, it can be seen from the data in Fig. 5 that a noteworthy between-group statistical discrepancy ($Z = -2.61$, $P_{bonf} = 0.027$) was observed in the GEV of microstate E at Week 4. The rTMS group exhibited a significantly reduced GEV of microstate E [20.1 (11.8, 31.1)] in comparison to the control group [28.6 (25.2, 38.0)] (Supplementary table S5). As is shown in Fig. 6, further analysis revealed a significant negative correlation between individual GEV of microstate E and CRS-R scores ($r = -0.57$, $P_{bonf} < 0.001$). A remarkable negative correlation was also established between the coverage of microstate E and CRS-R scores ($r = -0.49$, $P_{bonf} = 0.002$).

4. Discussion

In this study, we find that the inclusion of a 4-week rTMS in conventional awakening therapy heightened the proportion of patients emerging improvement on LOC by nearly 29 % compared to standard interventions without rTMS. Furthermore, the distribution of LOC and CGI-I grades across the groups implied a trend that favored the rTMS group. Significantly, a majority of patients who exhibited a progression on LOC at Week 4 transitioned from a VS/UWS to an MCS. Given the lack of sensitivity of the GCS to discern these two LOCs (Bodien et al., 2021), this could account for the absence of statistical difference in GCS scores between the two groups.

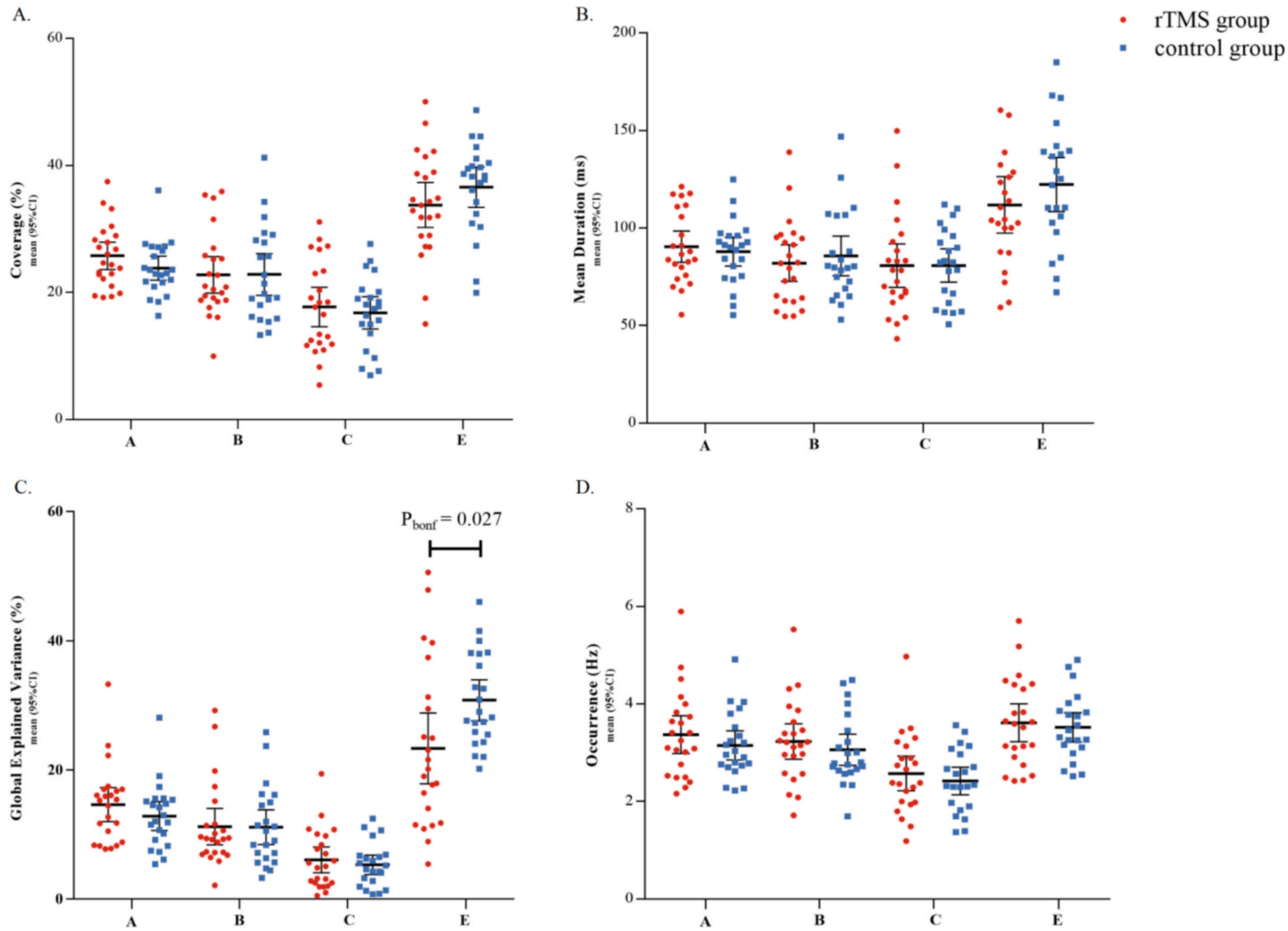

Fig. 5. Microstate features of the two groups at the end of the intervention Distribution of coverage of each microstate across groups; Distribution of mean duration of each microstate across groups; Distribution of global explained variance of each microstate across groups; Distribution of occurrence of each microstate across groups. *Abbreviations:* rTMS, repetitive transcranial magnetic stimulation.

Generally, this research provided favorable results supporting the application of rTMS as a valid awakening means. It is promising when contrasting the stimulation parameters with preceding studies that have yielded comparable positive results. In line with the previous studies (Zhang et al., 2021; Chen et al., 2022; Fan et al., 2022), high-frequency stimulation (≥5Hz) and DLPFC were simultaneously selected. On the one hand, neurons subjected to high-frequency stimulation would undergo long-term potential (LTP), which in turn manifest as enhanced cortical excitability (Hoogendam et al., 2010; Pell et al., 2011). DLPFC, furthermore, acting as a critical part of FPN, significantly contributes to regulating environmental awareness, decision-making, and working memory, and repairing imbalances between different prefrontal cortex networks (Menon & D'Esposito, 2022). In addition, the study by Kabir et al. found that single-pulse TMS applied to the DLPFC can induce changes in the occurrence and transition of microstates (Kabir et al., 2024). Specifically, it increased the frequency of microstates C and D while decreasing the frequency of microstates A and B, suggesting that TMS can be used to modulate whole-brain neural network activity. Such findings imply that modulating the neuronal activity of the DLPFC might contribute to coordinate the dynamic interaction of cerebral functional networks in patients with DoC, thereby promoting the recovery of consciousness.

The microstate-based findings might further confirm our aforementioned hypotheses. Limited by the inconsistency of topographic maps at baseline and post-intervention, the comparability of the features of microstates at different time points was compromised. Interestingly, the microstate E and F, which differed from the canonical 4 types of microstate model previously identified (Koenig et al., 2002; Britz et al., 2010), were observed in the absence of microstate D. These two microstates had also been documented in literature. According to a study reported by Custo et al., seven distinct resting-state topographic structures, corresponding to microstates A to F (microstate C was divided into C1 and C2), were observed based on the EEG data obtained from 164 healthy participants (Custo et al., 2017). Of these, microstate E was generally considered to be associated with a part of DMN, manifested by activation in the middle frontal gyrus, anterior cingulate cortex, and posterior cingulate cortex. Bréchet et al. also reported this microstate through a task-initiated spontaneous mentation paradigm and found that its main activity area was located in the medial prefrontal cortex, playing an important role in personal significant information processing, mental simulation, and theory of mind (Brechet et al., 2019). On the other hand, microstate F is typically located in the right inferior parietal lobule and cerebellum. Given its strong activation in the cerebellum, Tarailis et al. speculated that it might be related to the somatosensory network (Tarailis et al., 2024). Considering that microstates E and F constitute only a small fraction of the GEV in EEG data from healthy individuals, this may explain their lack of representation in the canonical four-class microstate model.

It is noteworthy that the absent microstate D is conceived to be associated with the dorsal attention network (DAN), which in charge of

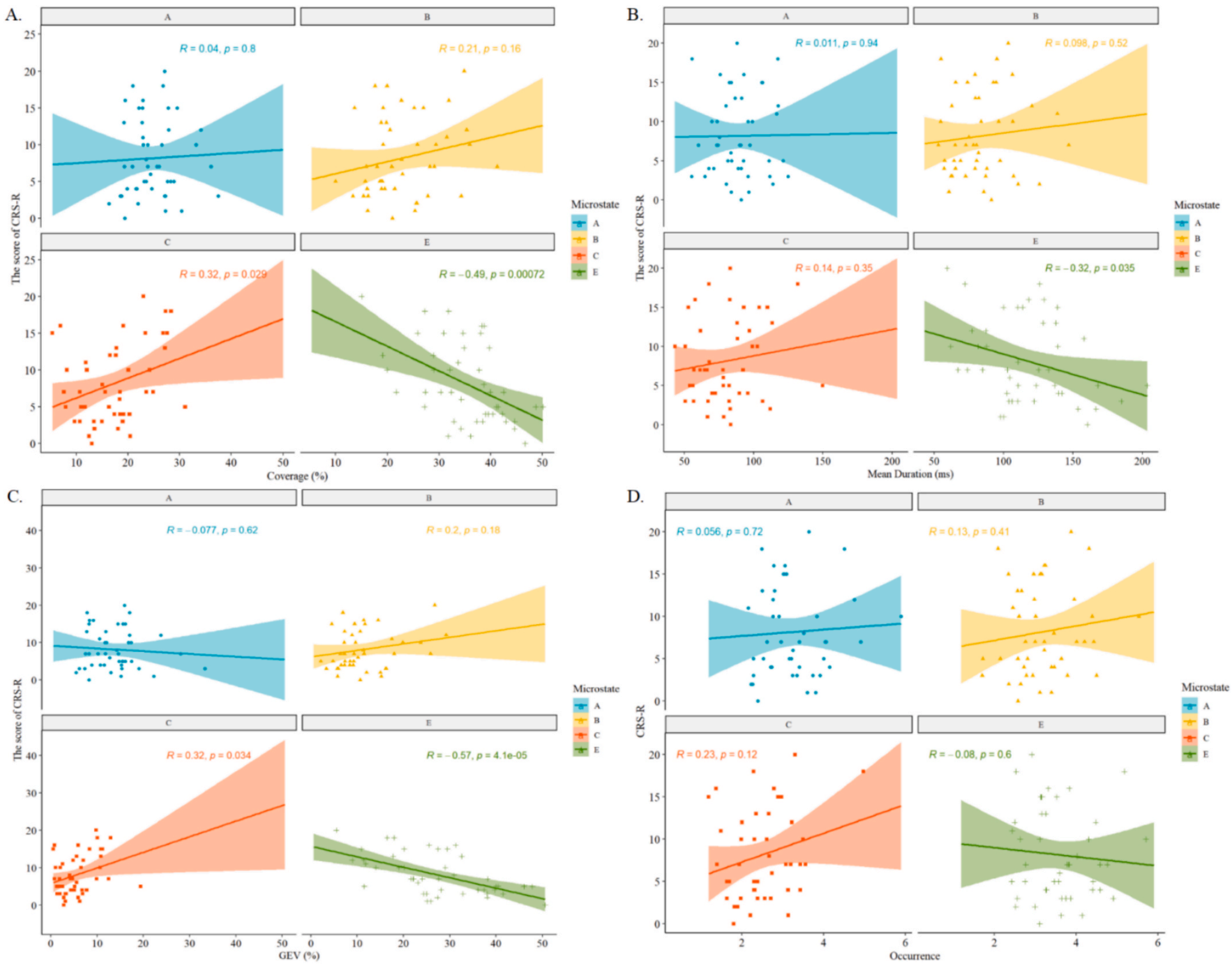

Fig. 6. The correlation analysis between the features of each microstate and corresponding individual CRS-R* * P values were not applied by bonferroni correction A. Correlation between individual coverage of each microstate and the total score of CRS-R; B. Correlation between individual mean duration of each microstate and the total score of CRS-R; C. Correlation between individual global explained variance of each microstate and the total score of CRS-R; D. Correlation between individual occurrence of each microstate and the total score of CRS-R. Abbreviations: CRS-R, coma recovery scale-revised.

top-down attention processes, characterized by voluntary target selection in task-driven events (Britz et al., 2010). In healthy people, the "extrinsic" networks (e.g., DAN) are negatively correlated with "intrinsic" networks (e.g., DMN) and maintain a dynamic balance (Fox et al., 2005). Existing studies have suggested that the recurrence of interaction within intrinsic and extrinsic networks significantly conduces to the restoration of consciousness (Threlkeld et al., 2018). Interestingly, the temporal parameters of these microstates have also been recognized as being closely associated with the balance of brain networks across various neuropsychiatric disorders (Tarailis et al., 2024). In this study, we found that the GEV and coverage of microstate E were significantly negatively correlated with the CRS-R scores of patients. Considering the absence of microstate D (i.e., relative low GEV), one possible explanation for this negative relationship is that in patients with more severe consciousness impairment, the DMN becomes hyperactive, subsequently suppressing the activation of the DAN. Hence, the presence of microstate E/F and the absence of microstate D observed in this study could potentially indicate a certain level of imbalance between these cerebral functional networks in patients with DoC.

Through comparing the parameter of different microstates at post-intervention across groups, a significant inter-group disparity was found in GEV of microstate E. The GEV represents the ability of a microstate to interpret comprehensive electroencephalogram (EEG) signals, with higher values indicating greater explanatory power and a stronger contribution to underlying neural activity. Therefore, the difference in the GEV of microstate E between the two groups may stem from changes in the activity of large-scale neural networks underlying their consciousness. This hypothesis was consistent with the results of a recent study that found the GEV of microstate E increased significantly in patients with reduced LOC (Ling et al., 2023). In addition, the microstate D was also found to be absent in their patients diagnosed with VS/UWS. Furthermore, the research by Li et al. reported the superior performance of mutual information functional connectivity network (MIFCN) based on microstate E in consciousness classification modeling. The results showed that the microstate E-based model outperformed other traditional microstate types in terms of sensitivity, specificity, and accuracy, suggesting a strong association between microstate E and level of consciousness (Li et al., 2024). Consequently, based on the significant between-group difference of GEV of microstate E in our study, it provides some tentative evidence that rTMS may get involved in modulating the balance between cerebral functional networks and promoting the recovery of consciousness in patients with DoC.

Notably, our findings did not establish a substantial linear correlation between the mean duration and occurrence of these microstates and the individual CRS-R score. This finding was in agreement with Artoni's research which discovered a particular "U-shape" (i.e., initial decreasing/increasing, subsequently ascending/descending) of microstate temporal dynamics parameters in subjects with increasing depth of sedation (Artoni et al., 2022). This might account for the lack of disparity observed in the mean duration and occurrence of microstate E across groups.

Contrary to prior drug-related clinical trials (e.g., amantadine) (Giacino et al., 2012), which reported a decline in the pace of consciousness recovery following cessation of treatment, persistent statistical differences across groups were observed in this study at follow-up. This finding parallels that of a previously similarly designed rTMS study where significant behavioral and electroencephalographic improvements in the intervention group were still noted at 30 days post-intervention follow-up (Zhang et al., 2021). An implication of this finding is that the LTP effect might not disappear immediately after intervention. However, this hypothesis must be confirmed through longer-term follow-up. Due to the limited duration of patient hospitalization, it is challenging to obtain accurate clinical behavioral scale scores and neurophysiological data from discharged patients. As a result, further empirical exploration is required to conclusively substantiate this interpretation.

This study acknowledges certain limitations. While the CRS-R has been employed as the "gold standard" for measuring LOC, its results might exhibit bias due to potential sensory, cognitive, or motor impairments in patients with DoC. Nevertheless, the credibility of the study results is strengthened by supplementing the neurophysiological evaluation based on EEG microstate. Besides, it must be acknowledged that the GEV has limitations when used to evaluate the temporal series activity of microstates. Therefore, the potential clinical significance of this parameter should be interpreted with caution. Finally, the lack of MRI scans from patients may induce variations in source space imaging of microstates. Given the common manifestation of multi-system complications in patients with DoC, it may be challenging to require them to endure the program of MRI. Despite this, considering the high similarity between the microstate topographic structure and respective source space imaging with prior research, the corresponding resting-state functional network of each microstate appears to retain a significant degree of credibility.

5. Conclusion

The administration of a 4-week regimen of high-frequency rTMS over the DLPFC combined with conventional awakening therapy for patients with DoC provides potential promotion in recovery of consciousness. Microstate analysis suggests that rTMS might get involved in modulating the balance among cerebral functional networks and promoting the recovery of consciousness in patients with DoC.

CRediT authorship contribution statement

Zhenyu Liu: Writing – original draft, Investigation, Formal analysis. **Shanshan Wu:** Writing – review & editing, Supervision, Methodology. **Shuwei Wang:** Writing – review & editing, Validation, Methodology. **Huijuan Wu:** Writing – review & editing, Validation, Conceptualization. **Hongliang Gao:** Writing – review & editing, Methodology, Conceptualization. **Xiao Lu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103802.

Data availability

Data will be made available on request.

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